

Brain metastases in lung cancer. Impact of prognostic factors on patient survival

Uroš Smrdel, Matjaž Zwitter, Viljem Kovač

Department of Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background. Brain metastases are common patterns of dissemination in lung cancer patients. In this paper we would like to assess the pattern of brain metastases in lung cancer patients and the impact of prognostic factors on the survival of lung cancer patients with brain metastases.

Patients and methods. In the year 1998 there were 974 registered patients with lung cancer in Slovenia, six hundred and fifteen of them were treated at the Institute of Oncology Ljubljana and we analyzed them. Among 615 patients 137 (22.3 %) of them have had brain metastases during a natural course of disease.

Results. For 12 patients presenting with solitary brain metastases (most of them were undertaken metastasectomy) median survival was 7.6 months, while in patients with multiple brain metastases the median survival was 2.8 months ($p = 0.0018$). Of the 137 patients 45 (32.8 %) were small cell lung cancer patients, 43 (31.4 %) were adenocarcinoma patients and 19 (13.9 %) were squamous cell carcinoma patients. Patients with performance status (WHO scale) less than 2 had the median survival time 3.7 months while patients with performance status 2 or more had median survival time 2.7 months ($p=0.0448$).

Conclusions. Patients with solitary brain metastases had better survival comparing with those who had multiple metastases. It is surprisingly that the portion of brain metastases patients with adenocarcinoma is almost equal to those with small-cell lung cancer therefore, the prophylactic cranial radiation becomes actual for both groups of patients. The performance status of patients with brain metastases remains very important prognostic factor.

Key words: lung neoplasms; brain neoplasms secondary; survival analysis

Introduction

Brain metastases are common patterns of dissemination in lung cancer patients. In the natural course of disease in around 17% of patients with squamous carcinoma, in 24% of patients with anaplastic carcinoma, in 39% of patients with adenocarcinoma and in 42% with small cell carcinoma brain metastases will develop.¹ Admittedly non-small cell car-

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Correspondence to: Uroš Smrdel, M.D., Department of Radiotherapy, Institute of Oncology; Zaloška 2, 1000 Ljubljana, Slovenia; Phone +386 1 5879 622; Fax +386 1 5879 400; E-mail: usmrdel@onko-i.si

cinoma of the lung patients with single resectable metastases will gain from metastasectomy followed by the external beam cranial irradiation.²⁻⁴ In those patients a gain can be objectified as the survival. Unfortunately, those patients represent only about 10% of lung cancer patients with brain metastases. The rest 90% of lung cancer patients are either small cell lung cancer patients or patients with multiple or irresectable metastases which do not benefit from the same treatment.

The majority of patients are thus offered the choice of palliative an external beam cranial irradiation or a corticosteroid treatment as the best supportive care.³ In last few years there is a tendency towards shorter radiation courses. There is evidence that the size and the number of fractions do not influence the outcome of treatment and duration of response.^{5,6} Furthermore, it seems that the only factor influencing the response is the severity of neurological deficit and that those patients presenting with the most severe deficit usually respond better than those with only minor neurological changes. On the other hand those presenting with minor neurological changes fare better in the term of survival, which is expected.^{7,8}

An acceptable approach towards the treatment of brain metastases is corticosteroid therapy alone, which is particularly appropriate for those elderly in poor physical condition.⁹

At the Institute of oncology in Ljubljana we are currently using 5 x 4 Gy, 10 x 3 Gy, 12 x 2.5 Gy and 14 x 2.5 Gy. In this paper we would like to assess the pattern of brain metastases in lung cancer patients and the impact of treatment on the outcome of lung cancer patients with brain metastases.

Patients and methods

The Cancer registry of Slovenia collects data on all cancer patients in Slovenia. In the year

1998 there were registered 974 patients with lung cancer,¹⁰ six hundred and fifteen of them were treated at the Institute of Oncology Ljubljana. In the year 2003 we reviewed all these 615 patients who were at least once examined and managed at our Institute.

The median age of lung cancer patients was 62.66 years (min. 36.01; max. 89.54 standard deviation 10.029); male, female ratio was 4:1; histological types were: 155 (25.2 %) adenocarcinoma, 217 (35.3 %) squamous carcinoma, 32 (5.2 %) anaplastic carcinoma, 132 (21.5 %) small cell carcinoma, 45 (7.3 %) non small cell carcinoma, 10 (1.6 %) mixed carcinoma, 1 (0.2 %) bronchioloalveolar carcinoma. Twenty-one patients (3.4 %) had no histological diagnosis prior to their death.

Among 615 patients 137 (22.3 %) have had brain metastases during the natural course of disease.

Of these 137 patients 22 (16 %) presented with brain metastases at the time of a diagnosis and 115 (84 %) underwent a treatment and developed brain metastases later on.

Patients were treated for brain metastases either with radiotherapy alone (110 patients (80.3 %)) or in cases with solitary brain metastases with metastasectomy followed by radiotherapy (12 patients (8.8 %)). Due to a poor performance status 15 patients (10.9 %) received no oncological treatment except the best supportive care.

Results

The median survival for all 615 patients diagnosed with lung cancer in 1998 was 8.9 months (range: min. 2 days, max. 62.6 months; 95 % confidence interval 7.93 - 9.9 months).

For patients with brain metastases the median survival was 3.1 months (range: min 0 days, max: 52.2 months)

For 12 patients presenting with solitary

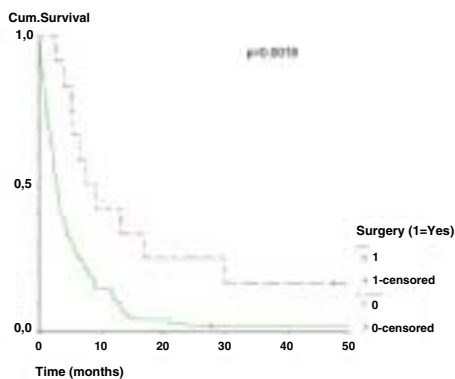


Figure 1. Surviving of patients with solitary brain metastases and patients with multiple brain metastases.

brain metastases (the most of them were undertaken metastasectomy), median survival was 7.6 months, (range: min 2.4 months, max 52.2 months, 95% confidence interval 2.9 - 12.4 months) compared to those with multiple brain metastases for whom the median survival was 2.8 months (range: min 0 days, max 50.4 months; 95% confidence interval 2.1- 3.5 months). The difference is statistically significant (log-rank $p = 0.0018$) (Figure 1).

Of the 137 patients with brain metastases 45 or 32.8 % were small cell lung cancer patients, 43 or 31.4 % were adenocarcinoma patients and 19 or 13.9 % were squamous cell carcinoma patients (Figure 2).

Predictably an important factor influenc-

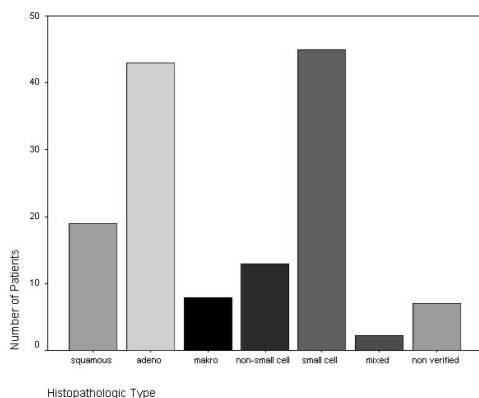


Figure 2. The histological type of lung cancer patients with brain metastases.

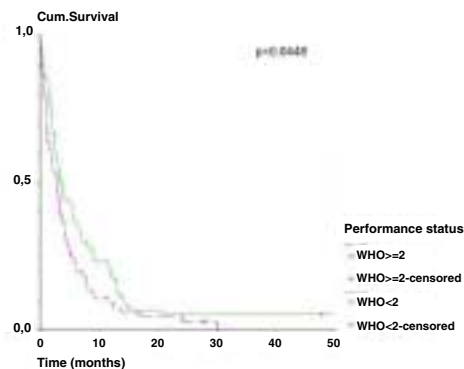


Figure 3. Survival of patients with brain metastases according to the performance status.

ing the survival in lung cancer patients with brain metastases is a performance status. In those patients with performance status on WHO scale less than 2 a median survival was 3.7 months while for patients with a performance status on WHO scale 2 or more a median survival was 2.7 months. This small difference is statistically significant with $p=0.0448$ (Figure 3).

There were 18 patients with adenocarcinoma confined to chest, later on presented with brain metastases, their median survival was 16.1 months (range: min 4.7 months max: 56.6 month) and their median survival after the diagnosis of brain metastases was 2.3 months (range: min. 0 days max 50.4 months)

Discussion

As already shown elsewhere¹ a fair proportion of lung cancer patients will be, during the course of their disease, presented with brain metastases. At our Institute 22.3 % of lung cancer patients reported in 1998 presented with brain metastases in the course of disease.

There was still a prevalence of squamous cell carcinoma in all patients, but in those with brain metastases, there is almost an equal proportion of small cell lung cancer and

adenocarcinoma (32.8 % and 31.4 % respectively). In most historical studies there was a well-established prevalence of squamous cell carcinoma,¹¹ but in last years we are starting to recognize a rise in adenocarcinoma patients.¹² In our retrospective of 155 patients with adenocarcinoma 43 or 27.7 % presented with brain metastases which is comparable with 45 of 132 or 34 % for non small cell lung cancer and far above 19 of 217 or 8.8 % for squamous carcinoma.

Since of 43 adenocarcinoma patients with brain metastases 18 or 41 % at presentation had a disease confined to chest and either received surgery or radiotherapy with curative intent, we could assume that with the increase in adenocarcinoma incidence there will also be the increase in the number of patients who will present with brain metastases after the radical treatment. This presumption opens space for screening for brain metastases in this patients and open question of prophylactic brain irradiation in adenocarcinoma patients.^{13,14}

For patients with solitary brain metastases the effective treatment is metastasectomy followed by brain irradiation, which in patients with good performance status yield a survival superior to irradiation alone.¹⁵ However, similar results are achieved with the use of cranial stereotactic radiosurgery.¹⁶

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